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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 17

Application Number: 09/447,490
Filing Date: November 23, 1999
Appellant(s): ECKARDT ET AL.

Gabriel P. Katona
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 10/2/00.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will have a bearing on the decision in the pending appeal, is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments after Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because it contains Applicants arguments concerning patentability of their application. The application concerns a process for making Carbamazine from dibenzo[b,f]azepine (iminostilbene) and cyanic acid. Carbamazine is an anti-convulsant first patented in 1960.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Applicants again are making arguments rather than stating

issues. One issue is whether claim 14 of Acklin (EP 277,095), now accurately translated from the original German, anticipates Applicants rejected claims. A second issue is whether Acklin (EP 277,095) as a whole or the corrected translation of Acklin (EP 277,095) makes obvious the *in situ* generation of cyanic acid in the Applicants' claimed process.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 2-8 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

EP 277,095	Acklin	3-1988

BPAI Decision in Appeal # 95-4841.

"Handbook of Chemistry and Physics, 42nd Edition", Charles D. Hodgman Editor, The Chemical Rubber Publishing Co., Cleveland, OH, 1962, p 1753-1754.

"Gmelins Handbuch der anorganischen Chemie, Kohlenstoff, Teil D 1", Dieter Koschel, Editor, Verlag Chemie, Weinheim, 1971, p 344.

Lowry and Richardson, "Mechanism and Theory in Organic Chemistry, 3rd Edition", Harper and Row, New York, 1987, p 199.

Ruff, F. and Csizmadia, I.G. "Organic Reactions, Equilibria, Kinetics, and Mechanism", Elsevier, New York, 1994, p. 60.

USPTO 2000-2843, July 14, 2000, Translation and correction of # PTO 95-4841 "Statement (Report) of Inspection/Quality Control", Koytcheff, John M.

(10) Grounds of Rejection

Rudolf Eckardt and Hans-Joachim Jansch filed application 08/275,025 on July 14, 1994. Their application was for a process for making Carbamazepine from dibenzo[b,f]azepine (iminostilbene). Carbamazepine is an anti-convulsant first patented in 1960. The 08/275,025 application was rejected on obviousness grounds by another examiner. The Board of Patent Appeals and Interferences upheld that rejection in Appeal No. 1996-1528. The obviousness rejection was over an English translation of Acklin et al (EP 0 277 095 A1), published August 8, 1988. The original of Acklin is in German.

On November 23, 1999 Rudolf Eckardt and Hans-Joachim Jansch filed this present application 09/447,490 for the same process. The Applicants replaced claim 1 of the 08/275,025 application by the present claim 8. The first claim of 08/275,025 read "A process for producing carbamazepine which comprises reaction iminostilbene with alkali cyanate in acetic acid, or a mixture of aqueous acetic acid with water, or within alcohol and recovering the resulting carbamazepine." The current claim 8 differs from claim 1 in 08/275,025 by inserting the phrase "an acidic medium consisting of" before acetic acid, replacing "within" by "with", and adding the phrase "or with an aqueous alcohol". The net result is that there are now four rather than three possible solvents. These solvents are 1) acetic acid, 2) aqueous acetic acid, 3) a

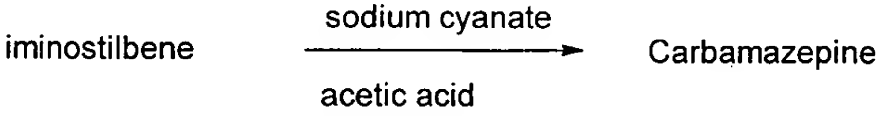
mixture of acetic acid and alcohol, or 4) a mixture of all three. Acetic acid is an acid so by definition all four solvents are acidic media. The present claim is thus slightly broader than the claim rejected by the board.

In a careful reading of the original German language patent Acklin (EP 277,095), the Examiner found a mistake in the English translation. A reference to "saures Mittel" in claim 14 of Acklin had been mistranslated "acidic acid" rather than "acidic agent". Based on this new translation (USPTO 2000-2843), which now places acetic acid as an agemt in the reference, a 35 USC 102(b) rejection was added to the previously affirmed 103(a) rejection.

The following ground(s) of rejection are applicable to the appealed claims:

a) 102(b) rejection over claim 14 of Acklin (EP 277,095)

Applicants process is sumarized in the following reaction scheme. They employ a mixture of sodium cyanate in acetic acid to convert iminostilbene to Carbamazepine. The sodium cyanate and acetic acid are reacted to from cyanic acid. In the present claims, acetic acid is part of all solvent choices and is used to generate the cyanic acid.



Claims 2-8 of the present application are rejected under 35 U.S.C. 102(b) as being anticipated or, in the alternative, under 35 U.S.C. 103(a) as obvious over Acklin (EP 277,095). The translation of the Acklin reference was discussed above. Acklin (EP 277,095) discloses conversion of iminostilbene to Carbamazepine using cyanic acid and the production of cyanic acid from sodium cyanate. Working examples 1-3 in the lines spanning 61 of column 4 to 31 of column 5 of the reference disclose one step processes for reacting sodium cyanate and iminostilbene to make Carbamazine.

Claim 14 of Acklin (EP 277,095) reads in the German "dass man als saures Mittel und gleichzeitig als Losungsmittel Essigsaure verwendet." Line 54-56 of page 16 of the original English translation reads "that the acidic acid and the solvent are acetic acid". This does not make grammatical nor chemical sense and the "acidic acid" phrase is redundant. This is the result of a typo made in the 1995 translation regarding "saures Mittel" in the English translation. The phrase "saures Mittel" is "acidic agent" not "acidic acid".

The new accurate translation of claim 14 of Acklin (EP 277,095) from lines 17-18 of page 6 of USPTO 2000-2843 is:

> "acetic acid is used as acidic agent, and concurrently as solvent."

Note that "agent" replaces "acid" and "concurrently" has been added. In column 2 line 63 and column 3 line 4 of Acklin (EP 277,095), the same phrase "sauren Mittels" (acidic agent) appears. In line 23 "saure katalytishe Mittel" and in line 27 "saures Mittel" appear in the German original. In these cases but not in claim 14, "Mittel" has been correctly translated "agent". This is on page 6 of the original English translation in lines 6, 10, 25, and on page 7 line 3.

Thus, no other acid is required by claim 14 of Acklin (EP 277,095) because acetic acid does the job of both acidic agent and solvent.. A process chemist, upon reading Acklin (EP 277,095) would realize that an acidic agent is taught by the reference as required to generate cyanic acid from its salt. The word "concurrently" makes clear that the reference possessed the concept of generating the cyanic acid and performing the reaction on iminostilbene at the same time, where the acetic acid functions as both solvent and acidic agent. Thus, claim 14 would be understood as using acetic acid as 1) solvent, and 2) the agent to react with sodium cyanate (disclosed in working examples 1-3 in the lines spanning 61 of column 4 to 31 of column 5 of the reference) to generate the cyanic acid which is actually what reacts with the iminostilbene.

Acklin (EP 277,095) teaches not only using acetic acid as the catalyst and as solvent, as set forth by the Board of Patent Appeals and Interferences (Appeal #

95-4841), but also teaches acetic acid as the sole acidic agent. Claim 14 of Acklin (EP 277,095) teaches that the disclosed process is not limited to the preferred acidic agents i.e. formic acid or stronger. Hence, all elements of applicants' process are present, including use of acetic acid as the acidic agent.

i) Anticipation of claims 2-4

Regarding claims 2-4 of the present application, on page 4 line 25 of the translation, Acklin teaches carrying out the reaction in "mostly water- alcohol- and amine-free" conditions. Since we do not know what "mostly" means it is clear a few percent of these substances may be present in a suitable solvent. Claims 2-4 of the present application includes the range zero to a few percent water or alcohol.

ii) Anticipation of claim 5

Regarding claim 5 of the present application, Acklin (EP 277,095) teaches using alkali cyanates. Example 2 of Acklin teaches a process comprising adding NaOCN to iminostilbene in acetic acid.

iii) Anticipation of claim 7

Regarding claim 7 of the present application, in lines 62-63 of column 1 Acklin (EP 277,095) teaches that preferred salts are sodium and potassium.

b) 103(a) Rejection over either Acklin (EP 277,095) or the translation

Alternatively, claims 2-8 of the present application are rejected under 35 U.S.C. 103(a). Applicants' process is obvious for reasons affirmed by the Board of Patent Appeals and Interferences (Appeal # 95-4841). Applicants have not narrowed their claim language in any manner. Nor have Applicants asserted that the present claims have been narrowed. Applicants present no specific reasons as to why the previous decision by Board of Patent Appeals and Interferences was faulty.

The new "acidic medium" language, not present in the 08/275,025 application, does not distance applicants claims from the reference as 1) Acklin used an acidic medium and 2) the medium in the rejected claims of 08/275,025 was always acidic. All of Applicants' claimed elements are present in Acklin (EP 277,095).

i) Obviousness of claims 5 and 8

Claims 5 and 8 of the present application are rejected under 35 U.S.C. 103(a) as being unpatentable over Acklin (EP 277,095). Claim 14 is not the only teaching of Acklin (EP 277,095) bearing on the current application. The second and third paragraphs of page 4 of the English translation describe production of the required cyanic acid by treatment of an alkali cyanate with an acid and that acetic acid is a suitable solvent for the reaction with iminostilbene.

Working examples 9 and 10 spanning pages 13 and 14 of the translation teach reaction of iminostilbene with cyanic acid in acetic acid with no additional acids present. This would render obvious preparing the cyanic acid *in situ*. Claims 5 and 6 of Acklin (EP 277,095) teach releasing and using cyanic acid from alkali cyanates without isolating the cyanic acid. Dependant claim 7 of Acklin (EP 277,095) teaches doing the release of cyanic acid in acetic acid. Regarding claim 5, changing the order of addition is an obvious variation to one of ordinary skill in synthetic organic chemistry.

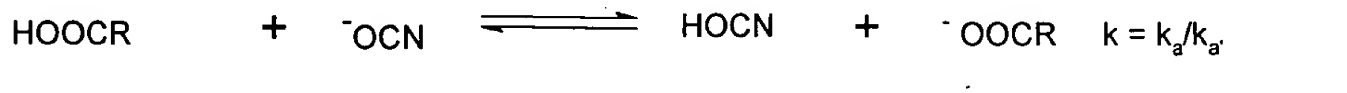
(11) Response to Arguments

a) Attorney states in line 3 of page 3 of his substitute brief "As no accurate translation of Acklin et al is available ... ". This is not correct. In paper 13 an accurate translation of Acklin (EP 277,095), USPTO 2000-2843, that corrected earlier errors was sent to Applicants.

b) Attorney argues in the sentence bridging pages 2 and 3 of his substitute brief that acetic acid is "not capable of liberating cyanic acid from its salts". In lines 16-17 on page 5, Attorney argues "acetic acid is also a weaker acid than cyanic acid, which it, therefore, can not liberate from its salts". Acklin (EP 277,095) teaches acetic acid explicitly in claim 14. The two paragraphs spanning line 54 of column 1 to line 16 of column 2 describe production of the required cyanic acid by

treatment of an alkali cyanate with an acid and that acetic acid is a suitable solvent for the reaction with iminostilbene. Working examples 9 and 10 spanning line 27 to line 48 of column 6 teach reaction of iminostilbene with cyanic acid in acetic acid with no additional acids present. This would render obvious preparing the cyanic acid *in situ*. Claims 5 and 6 of Acklin teach releasing and using cyanic acid from alkali cyanates without isolating the cyanic acid. Dependant claim 7 of Acklin teaches doing the release of cyanic acid in acetic acid.

Furthermore, Acklin's (EP 277,095) teaching that acetic acid alone is sufficient is chemically reasonable. Attorney' argument is a fundamental misunderstanding of the concept of chemical equilibrium. The precise question is what is the equilibrium constant for the reaction of any acid and a cyanate salt. The answer depends on the strength of the acid involved. The reaction between a weak acid like acetic or formic acid and the salt of a weak acid like cyanic acid is:

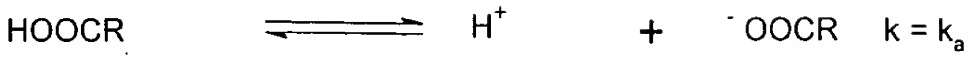


where R = H (formic acid)
or = CH_3 (acetic acid)

Cyanic acid

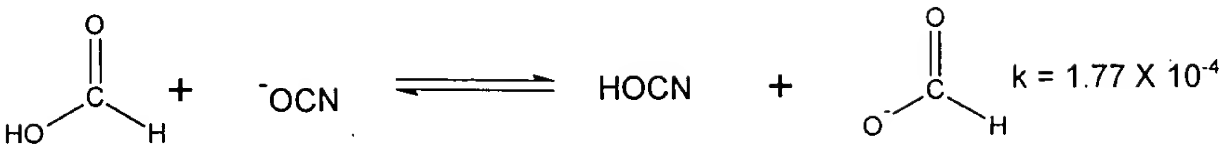
The constant k from above is derived from:

1) The dissociation of a weak acid

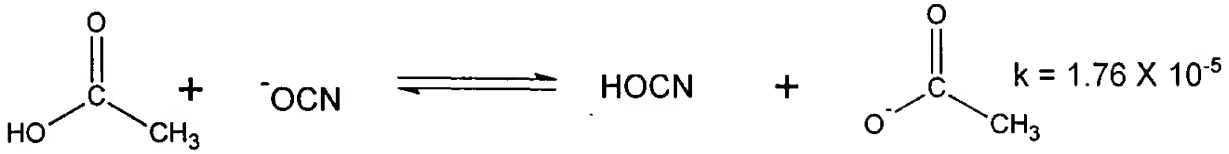


2) The association of cyanic acid

The law of mass action in chemistry requires that the equilibrium constant for the reaction between a weak acid and the salt of a second weak acid be the ratio of the dissociation constant of the weak acid (k_a) and the second weak acid ($k_{a'}$). The values of the dissociation constant given in pages 1753-1754 of the "Handbook of Chemistry and Physics 42nd Edition" and on page 344 of "Gmelins Handbuch der anorganischen Chemie, Kohlenstoff, Tiel D1" are acetic acid = 1.76×10^{-5}, formic acid = 1.77×10^{-4}, and cyanic acid = 2.0×10^{-4}. Using these numbers, the calculated equilibrium constants are 8.8×10^{-2} for acetic acid and 8.8×10^{-1} for formic acid.



Formic acid Cyanic acid



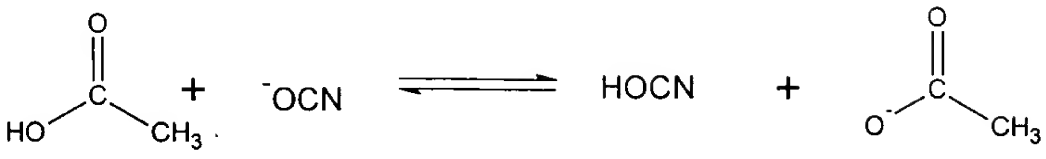
Acetic acid Cyanic acid

In acetic acid, a cyanate salt will be 8% converted to cyanic acid. In formic acid, a cyanate salt will be 47% converted to cyanic acid. Thus, both acids are sufficiently strong to form enough cyanic acid *in situ* but neither completely converts a cyanate salt to cyanic acid. Applicants' assertion that acetic acid is not capable of converting cyanate salts to cyanic acid is clearly incorrect. Formic acid is more potent but acetic acid is also capable of converting cyanate salts to cyanic acid and this is explicitly taught by the reference.

c) Attorney argues in the last paragraph on page 3 of his substitute brief that the reaction of applicants' process is between the iminostilbene substrate and cyanate salts and these alteration forms the heart of applicants' invention. In lines 3-4 of the final paragraph on page 3 he states "no cyanic acid (i.e. hydrogen cyanate) is involved in the herein claimed process". This is not persuasive because as pointed out above any mixture of acetic acid and a cyanate salt will generate cyanic acid at faster rate than any subsequent reaction that consumes the cyanic acid.

A mixture of a cyanate salt and iminostilbene will do nothing until an acid is present. This is taught by the reference in lines 30-39 of column 1. Applicants abstract makes clear that acetic acid is a necessary part of their process. Applicants' process can not involve a trimolecular complex among the iminostilbene, acetic acid, and the cyanate anion because this would violate the laws of chemistry. To quote from "Organic Reactions, Equilbria, Kinetics, and Mechanism"; [t]rimolecular reactions are very rare because the synchronous collision of three molecules is not very probable". The iminostilbene has no effect on the rate of cyanic formation or on the equilibrium constant of its formation.

The reaction between acetic acid and cyanate salts is, in practical terms, instantaneous with respect to the slower subsequent reaction of cyanic acid with iminostilbene. A concise analysis of the reaction kinetics is provided by the section titled "Preliminary equilibrium" on page 199 of Lowry and Richardson. Although the rate equation (2.97) for such a preliminary equilibrium process has three concentration terms, the laws of chemical kinetics make clear this does not mean that a collision among three molecules is involved in the rate-determining step. The first reaction pictured below is a proton transfer process and therefore the rate expected to be diffusion limited.



Acetic acid Cyanic acid

Cyanic acid

will be quickly generated and then consumed until the alkali cyanate is exhausted. The second reaction, involving the heavier atoms is both slower and not reversible. Acklin does not say that acids weaker than formic acid can not be used. In addition, claim 14 of Acklin's (EP 277,095) specifically describes acetic acid as a suitable acetic agent notwithstanding earlier comments about formic acid. Enough cyanic acid is formed in the equilibrium with acetic acid that the formation of the desired product proceeds at a useful rate.

d) Attorney argues that in lines 2-3 of paragraph 2 on page 4 of the substitute brief that "Acklin et al actually teaches away from the possibility of the presence of cyanic acid under the conditions herein claimed reaction". In the fourth paragraph on page 4, he writes "the present invention uses an entirely different reaction than that which takes place in Acklin et al". Attorney has misstated Acklin's (EP 277,095) teaching that "acetic acid is used as acidic agent, and concurrently as solvent."

The examiner requests the opportunity to present arguments at the oral hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

TCMcK
November 30, 2000

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